REMARKS

Claims 13-17 and 20-24 are pending and stand ready for further action on the merits. Support for new claims 22-24 can be found in the original disclosure. Support for the amendment to claim 21 can be found on page 2, lines 2-8 of the specification. No new matter has been added by way of the above-amendment.

I. Basic Terminology

It appears that the Examiner is confused regarding the concepts associated with the terms "osteoclastic activity" and "osteoclast formation". The Examiner seems to take the position that IFN-β inhibits the "osteoclastic activity" rather than inhibiting the "osteoclast formation". For example, the Examiner describes Applicants' invention in the last full sentence of page 2 of the outstanding Office Action as follows:

> As it is taught in the instant specification, IFN-β inhibits osteoclastic activity to result in increased bone density.

However, both of these terms are used to define different concepts. The term "osteoclastic activity" relates to the functional potential of mature osteoclasts. In other words, it

relates to the activity of mature osteoclasts to resorb the calcified matrix of bone via the secretion of acid. This is in distinction to the term "osteoclast formation" which refers to a kinetic process which includes a proliferation step, differentiation step and a maturational step from the precursor mononuclear cells present in the bone marrow and peripheral blood. The difference can be clearly seen in Table 1 of G.D. Roodman (Calcif. Tissue Int., Vol. 53, S94-S98, 1993 cited by the Japanese Patent Office in the search report of the parent application, PCT/JP96/02099) and Figure 8 of Sato (Endocrinol., Vol. 133, 397-404, 1993, a copy is attached hereto for the Examiner's review).

Since these terms define different concepts, it naturally follows that there are different methods used to measure each. To measure "osteoclastic activity," a pit formation assay is used, and to measure "osteoclast formation," a bone marrow cell culture system is used. Well known agents which act on the "osteoclastic activity" of mature osteoclasts are **omeprazol**, a specific inhibitor of H^+-K^+-ATPase (J. Tuukkanen and H.K. Vaananen, Calcif. Tissue Int., Vol. 38, 123-125, 986, attached hereto for the Examiner's review) and **sulfonamide**, a specific inhibitor of carbonic anhydrase (C. Minkin and J.M. Jennings, Science, Vol.

176, 1031-1033, 1972, attached hereto for the Examiner's review) except for calcitonin.

In the present application, the inventors have not examined the "osteoclastic activity" of IFN-β. Accordingly, Applicants have been careful to take steps to use these terms in accordance with their recognized definition.

Another important concept which the Examiner should keep in mind when evaluating the present invention, is the fact that the life span of a mature osteoclast is very short (K. Saotome et al., J. Jap. Orthop. Ass., Vol. 56, 777-789, 1982; A. Shioi et al., Calcif. Tissue Int., Vol. 55, 387-394, 1994, both articles are attached hereto for the Examiner's review).

Saotome et al. teach in the Abstract that:

> The osteoclasts are destined to extinction after about two to three weeks of life span.

Similarly, Shioi et al. teaches that osteoclasts formed in murine bone marrow cell culture systems have a short life span. In the Abstract, Shioi et al. teach:

> We find that 10^6 fractionated murine marrow cells enriched, for marrow-residing colony-forming units (CFU-CS), yield 3000-4000 tartrate-resistant acid phosphatase (TRAP)-expressing multinucleated giant cells when cultured for 12 days with ST-2 stromal cells. ...These

> cells continue to respond to calcitonin and survive for 24 hours in the absence of ST-2.

Thus, it would be clear to the skilled artisan that a continuous formation or supply of osteoclasts through the process of proliferation, differentiation and maturation is a crucial event for osteoclastic osteolysis in bone metabolism. Accordingly, the skilled artisan would recognize that an inhibiting agent for osteoclast formation, without deleterious side effects, would be a beneficial drug for osteoclast related bone diseases. A known example is bisphosphonate, which is described in the article of Coleman and Purohit (R.E. Coleman and O.P. Purohit, Cancer Treatment Reviews, Vol. 19, 79-103, 1993, attached hereto for the Examiner's review). Coleman et al. teach on page 87, beginning at line 9, the following:

> Within a few days of starting bisphosphonate treatment, a decrease in osteoclast numbers can be demonstrated (48). The effect on the osteoclast is due to a number of factors, including a direct toxic effect of ingested bisphosphonate on the resorbing osteoclast (49) and an inhibition of the differentiation of osteoclast precursors into mature osteoclast (50).

As can be seen from the above statement, bisphosphonate has an affect on both "osteoclast formation" and "osteoclastic activity". As is shown by experimentation in the present

specification, IFN-β strongly inhibits the formation step of the precursor bone marrow cells into mature osteoclasts. Thus, one of skill in the art would easily recognize and expect a therapeutic benefit by using IFN-β to treat osteoclast related bone diseases which have been shown to be effectively treated with bisphosphonates.

Applicants have provided the above explanation to help the Examiner in appreciating the patentable distinctions between the presently claimed invention and the teachings of the cited art, and to appreciate the fact that the presently claimed invention is fully enabled by the present disclosure.

II. Issues Under 35 U.S.C. §112, first paragraph

Claims 13, 14 and 16-20 are rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection.

The Examiner has taken the position that the present specification does not reasonably provide enablement for a method of treating any osteoclast-related bone disorder. The Examiner does find that the present specification enables a method for treating an osteoclast-related bone disorder characterized by osteolysis as a result of stimulated osteoclast activity.

The Examiner notes that in the present specification, there: 1) is experimental evidence which shows that interferon β inhibits osteoclast formation and has little to no inhibitory effect on osteoblasts; and 2) is no experimental evidence which shows that interferon β *increases* osteoclast formation. The Examiner has taken the position that one skilled in the art would not know how to make or use interferon beta to treat an osteoclast-related bone disorder characterized by a reduction in the osteoclast activity. The Examiner cites Goltzman et al. (Cancer, 2000, Volume 88, Supplement, pp.2903-2908) for teaching that the osteoclast related bone disorder of prostrate carcinoma is characterized by a decrease in the **osteoclast activity** and/or increased osteoblast activity.

As mentioned above, the concept of "osteoclast formation" and "osteoclast activity" are distinct. Applicants have shown by way of experimental evidence, that IFN-β has an inhibitory affect on **osteoclast formation**. Thus, the reference cited by the Examiner, Goltzman et al., which teaches that prostate carcinoma is characterized by a decrease in the osteoclast activity, the inventive IFN-β which is an inhibitor of osteoclast formation, would be effective in treating prostate carcinoma even if this

disease is characterized by a relative decrease in osteoclast activity in the patient's bone remodeling balance.

Applicants respectfully submit that the experimental evidence in the present specification, coupled with that which is known in the art, provides sufficient enablement for the skilled artisan to make and/or use the present invention without undue experimentation.

II(a) Experimental Evidence in the Specification

In Figure 1 of the present specification, Applicants have shown by way of experimentation that IFN-β has an inhibitory effect on the formation of tartrate resistant acid phosphatase (TRAP) positive multinucleated cells in an *in vitro* bone marrow cell culture using the bone marrow cells prepared from ddY mice. Similar effects are shown in Figure 2 using bone marrow cells from C57BL/6 mice.

As mentioned above, a proliferation step is included in what the art defines as an "osteoclast formation" process.

Figure 7 is a graph of the results from experiments showing that IFN-β has a promoting effect on the calcification of murine osteoblast-like cell differentiation.

In using the mice model, the present inventors have shown that treatment of post menopausal osteoporosis with interferon beta is effective in reducing the decrease in bone density.

II(b) That which is known in the art

Before the inventive priority date, the skilled artisan recognized that various metabolic bone disorders were correlated with an over-production of osteoclasts. We now provide examples of some of these reports.

II(b)(i) For Rheumatoid Arthritis (RA)/Osteoarthritis

Matsuyama et al demonstrate that multinucleated giant cells, which are indistinguishable from osteoclast cells, were formed from RA synovial adherent cells judging from the enzyme marker (tartrate-resistant acid phosphatase) and the cell lineage, monocyte-macrophage (T. Matsuyama et al., Clin. Exp. Immunol., Vol. 98, 257-263, 1994, a copy is attached hereto for the Examiner's review).

Similarly, Shiozawa and Kuroki published a review titled "Osteoporosis in Rheumatoid Arthritis: A Molecular Biological Aspect of Connective Tissue Gene Activation" (S. Shiozawa and

Y Kuroki, Tohoku J. Exp. Med., Vol. 173, 189-198, a copy is attached hereto for the Examiner's review). The author describes in the Abstract, that

> Osteoporosis, especially the juxtaarticular osteoporosis of involved joints, is a characteristic manifestation of rheumatoid arthritis (RA). Histomorphometric studies suggests the existence of increased bone turn over in RA: impaired bone formation and heightened osteoclastic bone resorption.

Shimizu et al. (S. Shimizu et al., Arthritis and Rheumatism, Vol. 28, 25-31, 1985, a copy is attached hereto for the Examiner's review) examined quantitative histologic studies on the pathogenesis of periarticular osteoporosis of rheumatoid arthritis and compared this to osteoarthritis. Shimizu et al. describe in the Abstract that:

> Bone resorption was also increased in RA, as evidenced by increases versus OA in percent total resorptive surface, percent active resorptive surface, and number of osteoclasts.

As the authors describe in the Discussion section on page 29, second paragraph, even under a condition of osteopenia, both the bone formation and resorption increased in rheumatoid arthritis. The increased bone formation was suggested by increased active osteoid (unmineralized)

surface. Applicants will discuss the "reactive bone formation" in further detail in section II(f) below.

Thus, rheumatoid arthritis/osteoarthritis is a osteoclast-related bone disorder.

II(b)(ii) For Paget's disease

Rebel et al describe in the Introduction section on page 344, (A. Rebel et al., The Lancet, August 16, 344-346, 1980, a copy is attached hereto for the Examiner's review) that:

> Paget's disease is a common disease of bone characterized by extensive histological change, among which is the presence of numerous giant multinuclear osteoclast, which contributes to a spectacular increase in the rate of bone resorption.

Thus, Paget's disease is a osteoclast-related bone disorder.

II(b)(iii) For Osteoporosis

There are many reports concerning this diagnostic disease accompanying a post menopausal event, rheumatoid arthritis, and periodontal disease, as well as others. Accordingly, the skilled artisan would be aware that osteoporosis is produced by osteoclasts capable of resorbing calcified-tissues. As such, osteoporosis is a osteoclast-related bone disorder.

Applicants do not believe it necessary to supply the Examiner with an additional reference teaching this fact.

II(b)(iv) For Periodontal diseases

Puzas et al. is a review article covering the field of periodontal diseases (J. E. Puzas et at., Method in Enzymology, Vol. 236, 47-58, 1994, a copy is attached hereto for the Examiner's review). In the section entitled "Regulation of Osteoclastic Activity in Infection", Puzas et al. teach that the bone loss in periodontal disease is due to an imbalance in the normally coupled activities of osteoclasts and osteoblasts, see page 49. The authors state that:

> ...a substantial amount of information is available regarding the activation of osteoclasts in this disease.

Nishihara et al. teach that this disease is not only characterized by osteoclastic activation but also osteoclast formation (T. Nishihara et al., Infection and Immunity, Vol. 63, 1893-1899, 1995, a copy is attached hereto for the Examiner's review). Nishihara et al. describe, in the Abstract, that:

> The mechanism of osteoclast-like cell formation induced by periodontopathic bacterium Actinobaccilus actinomycestemcomitans Y4 (serotype b) capusular-polysaccharide (capsular-like polysaccharide) was examined in a mouse bone marrow culture system. When mouse bone marrow cells were cultured with A. actinomycetemcomitans Y4 capsular-like polysaccharide for 9 days, many multinucleated cells were formed. The multinucleated cells showed several characteristic features, including tartrate-resistant acid phosphatase (TRAP) and the ability to resorb the calcified dentine.

Thus, periodontal disease is a osteoclast-related bone disorder.

II(c) Conclusions drawn from Section II(b)

Thus, the diseases described in the presently-amended claim 14 are all osteoclast-related bone disorders, regardless of the fact that the root cause of each of the diseases differs; that is rheumatoid arthritis is an autoimmune disorder, osteoporosis is the result of a hormonal imbalance, and Paget's and periodontal diseases are infectious diseases.

From the viewpoint of short life span of osteoclast one of the skill in the art easily understand that the stopping or decreasing the new mature osteoclast supply by the IFN-β treatment would sooner or later terminate or decrease further

bone destruction. It is not difficult to reach this conclusion, because the principle is simple irrespective of the different types of bone diseases described above. Thus, one of the skill in the art could easily understand the appropriateness of treating the diseases in the amended Claim 14 with IFN-β therapy.

II(d) Root causes of the diseases

It is unclear whether the Examiner has rejected the inventive claims because Applicants have not shown that IFN-β is effective in treating the root cause of the diseases listed in the inventive claims. Applicants respectfully submit that it is improper for the Examiner to make such a determination thereby restricting the range of modality with IFN-β to bone diseases having a root cause of osteolysis as a result of stimulated osteoclast activity. Accompanying the treatment with IFN-β to reinstate bone volume, clinicians will do additional therapies to treat the root cause of the diseases. Most of the medicament used to treat the root causes of the diseases have side effects which will affect the clinician's decision of how to use IFN-β. Furthermore, from the view point of bone diseases themselves, clinicians meet various

stages of the diseases. Thus, it is improper for Applicants to suggest a suitable modality at this stage. It is very important to do safety clinical trials. Establishment or suggestion of a suitable modality should he done by a clinician. Applicants believe that there would not be an undue burden on the clinician to establish a suitable modality based on the teachings of the present specification coupled with that which is known in the art.

Even in the case of bisphosphonate treatment, Body describe in his report (J.J. Body, Bone, Vol. 13, S57-S62, 1992, a copy is attached hereto for the Examiner's review) on page S61, in the last paragraph of remarks that

> Several therapeutic and preventive trials of bisphosphonates for metastatic bone diseases have been or will be started in the near future. There is a long way to go before the optimal therapeutic schemes are established, but if the initial results are confirmed, this new therapeutic modality will be one of the major recent therapeutic advance in clinical oncology.

One skilled in the art would easily recognize how to establish and monitor the therapeutic benefit of IFN-β. Body also describes in his report, in the Diagnosis and Monitoring of Bone Metastases section, on page S58 that there are many ways to establish and monitor the abnormal bone region for

the therapy of metastatic bone disease-lesions as listed in Table III on page S60. Of course the monitoring methods are not restricted for the tumor-related bone disorder. The methods include scintigraphic, radiographic, biochemical, and histological techniques as described at line 1 in the "Diagnostic and Monitoring of Bone Metastases". These methods, especially radiographic (X-ray) and biochemical techniques (serum alkaline phosphatase as a marker of bone formation and urine deoxypyridinoline as a marker of bone resorption, both technique are employed in the present specification) are common and routine for one of the skill in the art.

II(e) Enablement of treatment of colon cancer or cancer of digestive tract

The Examiner includes claim 17 in the rejection under 35 USC 112, first paragraph.

In the applicants specification bone metastases of colon cancer is listed in Table 1 on page 2 and Table 2 on page 3 in the cited paper of Stroll and Parbhoo, on page 2, column 6, beginning at last line, and of gastrointestinal tumor is

listed in Table 4.2 on page 28 in the cited paper of Galasco et al. At the instant priority date, it was already recognized that a common feature of tumor related disorders, irrespective of the primary tumor species, is that osteoclasts increment in the metastatic loci (S. L. Teitelbaum and F. P. Ross, Laboratory Invest., Vol. 71, 453-455, 1994, a copy is attached hereto for the Examiner's review). Teitelbaum et al. describe, on page 453, left column, beginning at line 10, that:

> The mechanisms by which metastatic carcinoma destroys the skeleton have long remained undefined, but, as shown by Quinn et al. (1) in this issue of Laboratory Investigation, and others (2), cancer cells, per se, have limited, if any, capacity to degrade bone. Because osteoclasts are generally abundant in skeletal metastases and are often intimately associated with tumor, a reasonable hypothesis holds that when established in marrow, cancer cells recruit osteoclasts to their local environment.

Similar arguments were made by Coleman and Purohit. They describe in the "Future Prospects" section, on page 98 in paragraph 3, beginning at line 5, that:

> Osteoclast activation by malignant cells is a fundamental step in the development of all bone metastases and inhibition of osteolysis by bisphosphonates has successfully inhibited the development of bone metastases in animals (107).

Actually Kulenkampff et al. (H. -Albrecht Kulenkampff et al., Virchows Arch (Pathol. Anal.) Vol. 409, 817-828, 1986, a copy is attached hereto for the Examiner's review) teach that bone metastases are divided into three stages for primary tumors having various origins, including breast cancer, renal cancer, bronchial carcinoma, myeloma, thyroid carcinoma, prostate carcinoma, cervical carcinoma, linguial carcinoma, histiocytoma of thyroid gland and unknown origin (See Table 1 of the report, on page 819). The three stages are described in the Summary section on page 817 as follows:

> The first stage is 'phase of early appearance' and no bone resorption takes place. The stimulation of osteoclastic resorption in the surroundings of tumor tissue is typical in the second' phase of interaction'. Pressure atrophy, aseptic necrosis and osteolysis by the tumor cells themselves are other mechanisms of bone destruction.

It is reasonable to expect that clinicians can easily distinguish the three stages by using their routine diagnostic and monitoring techniques such as X-ray diagnosis, urinary deoxypyridinoline measurement, serum alkaline phosphatase measurement, etc.

Further Kulenkampff et al. demonstrate that the increase of osteoclast number is a common feature of metastatic osteolysis by

qualitative and quantitative analysis irrespective of the primary tumor species. They describe, on page 822, at line 11, that:

> The number of osteoclasts per unit surface (OI; Ocl/cm) also increases. The combined osteoclast count from all cases examined was 57.6 ± 24.30 c1/cm. Compared with normal bone tissue (0I = 7.5 ± 5.2 Ocl/cm) a 7-fold increase is detectable.

Thus, it has been recognized that the involvement of osteoclasts, especially the formation of osteoclasts, is clear not only in the case of colon cancer and cancer of digestive tract but also other tumor species of various origin.

Actually, the osteoclasts are a target in bisphosphonate therapy of various types of metastatic bone diseases. The bisphosphonate acts on the stage of the formation and/or activation of osteoclasts (see the Coleman and Purohit report (R.E. Coleman and 0.P. Purohit, Cancer Treatment Reviews, Vol. 19, 79-103, 1993, a copy is attached for the Examiner's review). They describe, on page 87, beginning at line 9, that:

> Within a few days of starting bisphosphonate treatment, a decrease in osteoclast numbers can be demonstrated (48). The effect on the osteoclast is due to a number of factors, including a direct toxic effect of ingested bisphosphonate on the resorbing osteoclast (49) and an inhibition of the differentiation of osteoclast precursors into mature osteoclast (50).

Furthermore Quinn et al. describe in the CONCLUSION section on page 465 (J.M.W. Quinn et al., Laboratory Invest., Vol. 71, 465-471, 1994, a copy is attached hereto for the Examiner's review) that:

> Cells within the TIM population but not tumor cells are capable of differentiation into osteoclast-like cells which can resorb bone extensively. Both 1,25 dihydroxyvitamin D3 and bone stromal cells are necessary for this occurrence. TIM differentiation into cells capable of lacunae resorption could account for a component of the extensive osteolysis associated with carcinomatous skeletal metastases.

Quinn's work described above is done using human colon cancer (SW 480 and HT-29) and breast ductal type carcinoma (MDA-MD-435) adenocarcinomas and cervical (HeLa) squamous carcinoma. TIM means 'tumor-infiltrating macrophages' as is described on page 465, left column, beginning at last line.

Thus, based on the evidence of the inhibiting action of IFN-β on osteoclast formation as described in the present specification and its similar mechanistic pathway to bisphosphonate (Coleman and 0. P. Purohit), one of the skill in the art would easily recognize that the bone disorder resulting from metastatic colon cancer or cancer of digestive tract is a suitable target for interferon β therapy. As mentioned above, the suitable modality could be

decided by a clinician without undue burden using the common techniques.

Thus, one of the skill in the art could easily perform IFN-β based therapy for bone diseases caused by colon cancer or cancer of digestive tract based on the inhibiting activity of osteoclast formation by IFN-β.

To provide specific guidance for the modality of IFN-b treatment beyond the general discussion of the present specification may be more harmful than helpful in this field. It is generally accepted that cancer patients, especially those having cancer in the metastatic phase, are more serious clinically than compared to those of bone diseases having a metabolic, hormonal, and autoimmune background, described above. Suitable modality for IFN-β therapy should be established by clinicians.

Thus, one of the skill in the art could easily recognize that bone diseases caused by colon cancer or cancer of digestive tract are suitable targets for IFN-β therapy.

II(f) Enablement of treatment of prostate cancer

The Examiner has taken the position that one of skill in the art would not know how to use the instant method to treat bone

diseases induced by prostate cancer without undue burden based on the report of Goltzman et al.

In contrast to the Examiner's stand point, Applicants recognize that the bone diseases caused by metastatic prostate cancer are suitable targets for IFN-β therapy. This argument is based on the excellent property of IFN-β for promoting calcification according to the treatment conditions described in Example 6 of the present specification. Abnormal bone metabolism caused by metastatic prostate cancer is classified as a high turnover type in which both osteoclastic osteolysis and bone formation increases under an abnormal coupling balance.

The high osteolytic reaction is produced by the increased osteoclasts. Therefore, one of the skill in the art could easily recognize that the observed osteolytic response would be terminated or decreased by the inhibiting action of IFN-β on osteoclast formation as the first step response in IFN-β therapy. Actually, Coleman and Purohit describe, on page 91, beginning at line 5, that:

> Preliminary studies in men with advanced prostate cancer have suggested the bisphosphonates are

> effective in decreasing the high bone turnover seen in this diseases.

Undoubtedly the decrement of high bone turnover in bisphosphonates therapy is accompanied with a decrease in the reactive new bone formation based on the well known coupling theory (A.M. Parfitt, Calcif Tissue Int., Vol. 36, S37-S45, 1984, a copy is attached hereto for the Examiner's review). At the site of osteoclastic resorption a variety of growth factors and cytokines are released from the bone matrix, and these participate in new bone formation (L.G. Raisz, J. Bone Min. Res., Vol.8, S457-S465 1993, a copy is attached hereto for the Examiner's review). It is not difficult to expect that the termination or decrease of osteoclast formation by IFN-β results in the reduction of the growth factors and cytokines. This effect is actually observed in the case of bisphosphonate therapy described above.

However, bisphosphonate therapy is associated with another problem. The problem is insufficient calcification. Coleman and Purohit describe, on page 87, beginning at line 25, that:

> Etidoronate, particularly, will impair the mineralization of normal calcified tissues such as bone, cartilage and dentine (54). On the other hand,

> chlodoronate and aminobisphosphonates have relatively little effect on in vivo mineralization (55).

Goltzman et al. teach that the bone tissue of prostate carcinoma metastases has a rapid bone formation with insufficient mineralization. Goltzman et at describe in the paper on page 2907, in Oncogenous Hypophosphatemic Osteomalacia that

> Osteomalacia may occur when bone formation induced by tumors, such as prostate carcinoma, is so rapid that mineralization lags behind.

In view of the foregoing, one of the skill in the art can easily expect an advantage of IFN-β therapy with the reasonable expectation of the following steps:

First step: cessation or decrease of mature osteoclast supply will prevent the further osteolytic response.

Second step: lack or decrease in the number of mature osteoclasts will decrease the release of the growth factors and cytokines embedded in the bone matrix, and the rapid growth of osteoid tissue (insufficient mineralization tissue) will be down-regulated.

Third step: slowing down of the growth rate for osteoid formation is a key to restoring normal mineralization, and IFN-β

will promote the normal mineralization based on Example 6 in the specification.

The calcification promoting activity of IFN-β is independent of the other functioning cells in the bone tissue, as was demonstrated using a clonal cell line of osteoblasts MC3TS-E1 alone (Example 6 in the present specification). Applicants previously argued and emphasized the importance of a mineralization step in the present specification in comparison to a strong calcification inhibiting activity of IFN-γ and summarized as follows in the BACKGROUND ART section on page 3, column 4, beginning at line 31:

> Thus, in order to be a drug effective for therapy of bone disorders, especially the bone disorders requiring increase bone volume, the fact that the drug or the substance exhibits inhibition of bone resorption is insufficient, but the fact that the drug or the substance does not inhibit at all or only slightly inhibits the bone formation system (proliferation, differentiation and mineralization of osteoblasts), or preferably, the fact that the drug activates the bone formation system, must be proved.

It is reasonable to expect that a suitable modality should be done by clinicians themselves on a case-by-case

basis taking into account the individual patient's condition. The modality would depend on the clinical stage of the disorder. The variety in clinical stages of the prostate cancer related bone disorder is depicted by Goltzman et al., on page 2904 and Figure 1 (reference cited by the Examiner).

Thus, one of the skill in the art could easily recognize that the bone disorder caused by prostate cancer is one of the suitable targets for IFN-β therapy.

II(g) Conclusion

Thus, there is considerable direction and guidance in the specification, there is a high level of skill in the art at the time the application was filed, and all the methods needed to practice the invention are well known. Therefore, Applicants respectfully submit the test of enablement has been met, i.e., that one reasonably skilled in the art could perform the inventive method without undue experimentation. Please note that a patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 18 USPQ 2d 1331, 1332, (Fed. Cir. 1991). The fact that some experimentation is required is not fatal, so long

as an undue amount is not required. In re Geerdes, (CCPA 1974) 180 USPQ 789 .

Thus, in view of the comments above, Applicants respectfully request the rejection be withdrawn.

III Issues under 35 USC 103

Claims 13-21 are rejected by the Examiner under 35 U.S.C. 103(a) as being unpatentable over Manolagus (Bone, 1995) in view of Zawatzky et al (Journal of Virology, 1991, Vol. 65, pp. 4839-4846). Applicants respectfully traverse the rejection.

The Examiner has taken the position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to treat osteoporosis or bone disorders mediated by a decrease in gonadal hormones by the administration of IFN-β. Furthermore, one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Zawatzky et al on the negative regulatory effect IFN-β exerts on the production of IL-6 correlation of elevated IL-6 levels with bone resorption as taught Manolagus.

The Examiner cites the report of Manolagus report in which IL-6 is an essential pathogenetic factor in the bone loss caused by gonadal deficiency. However, at the time of the present invention, it was controversial whether IL-6 is a major factor for postmenopause osteoporosis.

III(a) Manolagus

Miyaura et al (C . Miyaura et al., J. Bone Min. Res., Vol. 8, S130, 1993, C. Miyaura et al., J. Bone Min. Res., Vol. 10, 1365-1373, 1995, a copy of each is attached hereto for the Examiner's review) argue that IL-1 α is a major endogenous bone resorbing factor in estrogen deficiency. Based on this, they added that other cytokines, such as IL-1 β and IL-6, may also be involved in the mechanism of bone resorption in OVX mice, but the contribution of these other cytokines is considered to be relatively **low**, see the Abstract in the 1993 article. In the 1995 article, Miyaura et al. teach on page 1372, in the last paragraph of the left column, that:

> In conclusion, estrogen deficiency stimulates the endogenous bone-resorbing activity of bone marrow fluids. A neutralizing antibody against IL-1 a completely suppressed the bone-resorbing activity.

> Antibodies against IL-6 and IL-6R also suppressed the bone resorbing activity, but only partially.

McKane et al. (W.R. McKane et al., J. Bone Min. Res., Vol. 9, 1313-1318, 1994, a copy is attached hereto for the Examiner's review) examined the circulating levels of cytokines that modulate bone resorption in women and analyzed from the view points of age and menopause. McKane et al. describe in the Discussion section, on page 1316 , in left column, at line 21, that:

> Thus, increased production of IL-6 could play a role in age-related bone loss in women. However, lack of correlation with the biochemical markers for bone turnover argues against this. The observed increase in IL-6 with age could be related to age-related changes in the immune system (24) rather than related to age-related changes in bone metabolism.

Further, McKane et al. describe on the same page, in the right column, at line 1, that:

> If cytokines are the major mediators of bone loss in aging or estrogen-deficient women, our negative findings are difficult to explain.

Incidentally, it should be noted that Pacifici (R. Pacifici, Endocrinology, Vol. 139, 2659-2661, 1998, a copy is attached hereto for the Examiner's review) describes in the report, on page 2660, in the right column, that:

> Whereas studies with transgenic mice and inhibitors of IL-1 and TNF have consistently demonstrated that IL-I and TNF are key inducers of bone loss in ovx

> animals, investigations aimed at assessing the contribution of IL-6 to ovx-induced bone loss have yielded conflicting results.

Thus, the status of IL-6 for post menopausal osteoporosis was still vague even at the time the claimed invention was made.

III(b) Zawatzky et al.

The results of Zawatzky et al. (1991) cited by the Examiner is more doubtful than Manolagous. Zawatzky et al. describe that IFN-β is a negative regulator for IL-6 production. But completely opposite results have been reported at the time of the claimed invention. Namely, there are many reports which conclude that IFN-β is a positive regulator of IL-6. Please notice that IFN-β2 is another name of IL-6 and IFN-β1 refers to IFN-β itself.

Kohase et al. (M. Kohase et al., Molecular and Cellular Biology, Vol. 7, 273-280, 1987, a copy is attached for the Examiner's review) describe in the Discussion section, on page 278, right column, that:

> The observation that rIFN-β^{117Ser} directly induced IFN-β2 expression, whereas IFN-α did not, suggests that although IFN-α and -β compete for the same cell

surface receptor (3), there can be differences in the intracellular events that they elicit.

Walther et al (Z. Walther et al., J. Immunol., Vol. 140, 974-977, 1988, a copy is attached hereto for the Examiner's review) also describe a similar result in the Discussion section, on page 976, right column at second paragraph, that:

> It is striking that the transcription of IFN-β2 gene is also enhanced by a cytokine such as IFN-β1 that inhibits cell proliferation. This is consistent with the earlier observation that IFN-β1 added in the presence of cycloheximide further increases the accumulation of IFN-β2 mRNA as judged by blot-hybridization analyses (14).

Rosztoczy and Content (I. Rosztoczy and J. Content, J. Interferon Res., Vol. 10, 637-645, 1990, a copy is attached hereto for the Examiner's review) describe in the Abstract, that:

> The results showed that human interferon-(HuIFN)-α, -β, and -γ at a concentration of 100-10,000 IU/ml enhanced the LPS-induced IL-6 production in the adherent cell fraction of PBMNC.

Wolvekamp et al. also attribute the increased production of IL-6 by IFN-β in the article entitled "Interteukin-6: historical background, genetics and biological significance" (see Table 1 on page 3, M.C.J. Wolvekamp et al., Immunology Letters, Vol. 24 1-10 1990, a copy is attached hereto for the Examiner's review).

Brod et al. (S.A. Brod et al., Neurology, Vol. 46, 1633-1638, 1996, a copy is attached hereto for the Examiner's review) also describe, in the Abstract, that:

> IFN-β1b (Betaseron) decreases CD3-mediated TNF-α secretion but increases another inflammatory cytokine, IL-6, that could potentially counteract its beneficial immunomodulatory effects.

Incidentally, there is a report in which IL-6 itself induces IFN-βmRNA (M. Bickel et al., Cytokine, Vol. 2, 238-246, a copy is attached for the Examiner's review). In the report, the authors clearly describe, in the Abstract, that:

> We first tested whether IL-6 could induce IFN-β mRNA. Using a reverse transcription/polymerase chain reaction procedure, we found that IFN-β mRNA was induced by IL-6.

Furthermore, Kohase et al. (M. Kohase et al., Cell, Vol. 45, 659-666, 1986, a copy is attached for the Examiner's review) describe, on page 659 at right column beginning at line 13, that:

> Nevertheless, several different polyclonal antibodies raised against recombinant IFN-β1 or recombinant IFN-β2 neutralized the biological activity of the heterogenous protein, and neutralizing monoclonal antibodies raised against recombinant or natural IFN-β1 also cross-neutralized IFN-β2 (Zilverstein et al., 1985; Rebel et al., 1986).

Based on the contradictory state of the art, the skilled artisan would not find that there would be a reasonable

expectation of success to treat bone related disorders with IFN-β.

The Zawatzky et al. work was published in 1991 and their study was almost the same as the previous works of Kohase et al (1987), Walther et al (1988), and Rosztoczy and Content (1990). However, Zawatzky et al never cited nor discussed these previous reports in which opposite conclusions had been argued. It is reasonable to think that one of the skill in the art would trust the conclusions of Kohase et al, Walther et al., and Rosztoczy and Content in this situation.

Any way, even at the time of the claimed invention, it is widely accepted that IFN-β (IFN-β1) is a positive regulator of IL-6 (IFN-β2) production in contrast to the Examiner's argument based on the teachings of Zawatzky et al.

Thus, one skilled in the art, in contrast to the position of the Examiner, would not extract any reasonable expectation that the present claimed invention is obvious nor would the skilled artisan be motivated to use IFN-b to treat bone disorders based on the ambiguous and unreliable work of Zawatsky et al. and Manolagus.

Applicants respectfully request that the rejection be withdrawn.

INFORMATION DISCLOSURE STATEMENT (IDS)

On October 12, 1999, Applicants timely filed an IDS enclosing a PTO-1449 form listing 12 documents. However, the Examiner returned the PTO-1449 form without initialing next to the entries of several of the documents. Accordingly, Applicants have listed these documents (and provided copies thereof) on the PTO-1449 form which is attached to the IDS enclosed herewith.

Conclusion

In view of the foregoing amendments and remarks, the invention as instantly claimed is in condition for allowance. A Notice to such effect is earnestly solicited.

In the event there are any additional matters remaining in this application, the Examiner is strongly encouraged to contact Garth M. Dahlen, Ph.D. (Registration #43,575), at (703) 205-8000 in order to discuss these matters.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time

for filing a reply in connection with the present application, and the required fee of $920.00 is attached hereto.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this concurrent and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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RCS/GMD/gh
0599-0158P
Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 18 and 19 have been cancelled.

The claims have been amended as follows:

Claim 14. (Three Times Amended)

The method for treating a patient having an osteoclast related bone disorder according to claim 13, wherein the disorder is selected from the group consisting of rheumatoid arthritis, Paget's disease, [rickets,] osteoporosis, [metabolic disorder, bone fracture,] osteomalacia, osteoarthritis, [osteogenesis imperfecta, diseases related to hormonal disorders, autoimmune disorders] and periodontal diseases.

Claim 21. (Amended)

The method for treating a patient having an osteoclast related bone disorder according to claim 20, wherein the bone disorder is postmenopausal osteoporosis.

Claims 22-24 have been added.